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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,689	10/31/2003	C. Frank Bennett	ISIS-5315	1919

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EXAMINER	
VIVLEMORE, TRACY ANN	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 03/31/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/698,689	BENNETT ET AL.	
	Examiner	Art Unit	
	Tracy Vivlemore	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 December 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *17,18,23-27 and 62-67* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *17,18,23-27 and 62-67* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/03 and 11/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election without traverse of group II, claims 17, 18, 23-27 and 62-67 in the reply filed on December 29, 2005 is acknowledged.

All claims to non-elected inventions have been canceled.

Information Disclosure Statement

The information disclosure statements filed December 2003 and November 2004 have been considered.

Oath/Declaration

The oath or declaration is defective. A new oath or declaration in compliance with 37 CFR 1.67(a) identifying this application by application number and filing date is required. See MPEP §§ 602.01 and 602.02.

The oath or declaration is defective because:
Non-initialed and/or non-dated alterations have been made to the oath or declaration. See 37 CFR 1.52(c).

The declaration of inventor Cowsert submitted May 24, 2004 contains non-initialed alterations.

Priority

No support can be found in applications 10/261,382 and 09/067,638 for use of CD40 antisense compounds to redirect splicing, reduce CD40 signaling or decrease IL-12 production. Thus the priority date given to these embodiments is September 30, 2003, the filing date of PCT/US03/31166. If applicant believes the prior applications provide support for these embodiments it should be pointed out with particularity in the response to this office action.

Specification

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01. Paragraph 151 contains a hyperlink.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 17, 18, 23-27 and 62-67 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the

application was filed, had possession of the claimed invention. This is a written description rejection.

The claimed invention is directed to methods of inhibiting expression of CD40, redirecting splicing of CD40 RNA, reducing CD40 signaling, or reducing IL-12 cytokine production in cells or tissues or to a method of treating an animal having a disease or condition associated with CD40 using antisense compounds that hybridize to a nucleic acid encoding CD40. The claims encompass use of antisense compounds that hybridize to and modulate expression of CD40 from any species.

The specification teaches antisense oligonucleotides directed to human CD40 and their use to inhibit CD40 expression in several cell lines. The specification also teaches peptide nucleic acids targeted to exon 6 of the murine CD40 mRNA and the use of these PNAs to change the ratios of alternatively spliced transcripts in cultured murine cells.

Neither the specification nor the prior art describes the structure of any antisense compounds that have function of hybridizing to and modulating expression CD40 from any species other than human and mouse. Additionally, the specification and the prior art do not teach the structure of any oligonucleotides that redirect splicing, reduce CD40 signaling or decrease IL-12 production from any species other than mouse.

The skilled artisan cannot envision the detailed structure of the encompassed antisense compounds that hybridize to CD40 from all species that are useful in inhibiting CD40 expression, redirecting splicing, reducing CD40 signaling or decreasing IL-12 production, regardless of the complexity or simplicity of the method of isolation.

Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it.

Claims 17, 18, 23-27 and 62-67 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for inhibiting expression of CD40 in a cell *in vitro*, does not reasonably provide enablement for inhibiting expression of CD40 in a cell *in vivo* in any organism. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The following factors as enumerated *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988), are considered when making a determination that a disclosure is not enabling: the breadth of the claims, the nature of the invention, the state of the prior art, the level of ordinary skill in the art, the level of predictability in the art, the amount of direction provided by the inventor, the existence of working examples and the quantity of experimentation needed to make the invention based on the content of the disclosure.

The invention of claims 17, 18 and 62-67 is directed to methods of inhibiting expression of CD40, redirecting splicing of CD40 RNA, reducing CD40 signaling, or reducing IL-12 cytokine production in cells or tissues using antisense oligonucleotides that hybridize to a nucleic acid encoding CD40. These claims have both *in vitro* and *in vivo* embodiments. The invention of claims 23-27 is directed to a method of treating an animal having a disease or condition associated with CD40 by administering an

antisense oligonucleotide that hybridizes to and inhibits CD40 expression. These claims have only *in vivo* embodiments and require a therapeutic outcome.

The specification teaches antisense oligonucleotides directed to human CD40 and their use to inhibit CD40 expression in several cell lines. The specification also teaches peptide nucleic acids targeted to exon 6 of the murine CD40 mRNA and the use of these to change the ratios of alternatively spliced transcripts in cultured murine cells.

Problems related to in *vivo* use of nucleic acids were well known in the art at the time of invention (see for example Opalinska et al. (Nature Reviews Drug Discovery, 2002, vol. 1, p. 503-514)). Such problems include the inability to specifically deliver an effective concentration of a nucleic acid to a target cell, such that a target gene is inhibited to a degree necessary to result in a measurable effect.

Opalinska et al. state on page 511

> "[I]t is widely appreciated that the ability of nucleic-acid molecules to modify gene expression *in vivo* is quite variable, and therefore wanting in terms of reliability. Several issues have been implicated as a root cause of this problem, including molecule delivery to targeted cells and specific compartments within cells and identification of sequence that is accessible to hybridization in the genomic DNA or RNA"

and in column 2 of the same page,

> "Another problem in this field is the limited ability to deliver nucleic acids into cells and have them reach their target. Without this ability, it is clear that even an appropriately targeted sequence is not likely to be efficient. As a general rule, oligonucleotides are taken up primarily through a combination of adsorptive and fluid-phase endocytosis. After internalization, confocal and electron microscopy studies have indicated that the bulk of the oligonucleotides enter the endosome-lysosome compartment, in which most of the material becomes either trapped or degraded."

Given this unpredictability, the skilled artisan would require specific guidance to practice the claimed methods *in vivo* in all organisms, with a resultant inhibition of gene expression or alteration of CD40 splice products, as claimed. The specification

provides examples of inhibition and alteration of splicing in cultured mouse and human cells, however, cell culture examples are generally not predictive of *in vivo* activity and the methods of delivery of the exemplified cell line would not be applicable to delivery of oligonucleotides to any organism. Due to differences in the physiological conditions of a cell *in vitro* versus *in vivo*, the uptake and biological activity observed *in vitro* would not predictably translate to *in vivo* results. Given these teachings, the skilled artisan would not know *a priori* whether introduction of oligonucleotides *in vivo* by the broadly disclosed methodologies of the instant invention, would result in the oligonucleotide reaching the proper cell in a sufficient concentration and remaining for a sufficient time to provide measurable activity of the nucleic acid.

The specification does not provide the guidance required to overcome the art-recognized unpredictability of using nucleic acids *in vivo* in any organism. The teaching of the prior art does not provide that guidance, such that the skilled artisan would be able to practice the claimed therapeutic methods.

Thus, while the specification is enabling for the examples set forth in the specification, the specification is not enabling for the broad claims of inhibiting the expression of CD40, redirecting splicing of CD40, reducing CD40 signaling or reducing IL-12 production in any organism as the art of modulating gene expression by introducing antisense oligonucleotides into an organism is neither routine nor predictable. The amount of experimentation required is such that one of skill in the art could not practice the invention commensurate in scope with the claims without undue,

trial and error experimentation and therefore, claims 17, 18, 23-27 and 62-67 are not enabled.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and In *re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 17 and 18 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2 and 18 of U.S. Patent No. 6,197,584. Although the conflicting claims are not identical, they are not patentably distinct from each other because the patented claims are a species of the instant generic claims and would thus serve to anticipate the instant invention. The patented claims are directed to antisense oligonucleotides targeted to human CD40 and their use in cells *in vitro* to inhibit expression of human CD40. The instant claims are directed to methods of inhibiting expression of CD40 from any species using antisense oligonucleotides and are thus generic to the patented species claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 17, 18 and 23-26 are rejected under 35 U.S.C. 102(e) as being anticipated by Stinchcomb et al. (US 6,194,150).

The claim invention is directed to methods of inhibiting expression of CD40 in a cell or tissue or treatment of a disease associated with CD40 using an antisense compound targeted to the nucleic acid encoding CD40. Diseases associated with CD40 include immune disorders and inflammatory conditions.

Stinchcomb et al. disclose antisense oligonucleotides and ribozymes targeted to CD40 and a method of inhibiting CD40 in cells using these nucleic acids; see claims 1 and 24. At columns 5-8 under the heading 'Summary of the invention' Stinchcomb et al. disclose that the methods of the invention can be used *in vivo* to treat disorders associated with CD40. At columns 1-5 Stinchcomb et al. disclose that disorders associated with CD40 include immune disorders such as organ rejection, and inflammatory disorders such as psoriasis.

Thus, Stinchcomb et al. disclose all limitations of and anticipate claims 17, 18 and 23-26.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein

were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 17, 18 and 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stinchcomb et al. as applied to claims 17, 18 and 23-26 above, and further in view of Mach et al. (PNAS 1997, vol. 94, pages 1931-1936).

Claims 17, 18 and 23-26 are described in the previous 102 rejection. Claim 27 recites that the method of treating an animal having a disease associated with CD40 can be used to treat a hyperproliferative disease such as cancer or atherosclerosis.

Stinchcomb et al. teach antisense oligonucleotides and ribozymes targeted to CD40 and a method of inhibiting CD40 in cells using these nucleic acids, see claims 1 and 24. At columns 5-8 under the heading 'Summary of the invention' Stinchcomb et al. disclose that the methods of the invention can be used *in vivo* to treat disorders associated with CD40. At columns 1-5 Stinchcomb et al. teach that disorders associated with CD40 include immune disorders such as organ rejection, and inflammatory disorders such as psoriasis. Stinchcomb et al. do not teach that CD40 is associated with cancer or atherosclerosis.

Mach et al. teach that CD40, which had been previously considered to be expressed mainly in T lymphocytes, is also expressed in human vascular endothelial cells, smooth muscle cells and macrophages. CD40 was found in all three cell types in

atherosclerotic lesions but not in uninvolved arteries, suggesting an association between CD40 signaling and atherosclerosis.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the method of treating a CD40 associated disease with CD40 antisense compounds taught by Stinchcomb et al. to treat a hyperproliferative disorder such as atherosclerosis. Stinchcomb et al. provide a motivation to use a CD40 antisense compound, teaching a relationship between CD40 and disease and further teaching that antisense compounds targeted to CD40 can be used to treat diseases associated with CD40 by modulating CD40 expression. Mach et al. provide a motivation to treat atherosclerosis by teaching that CD40 is associated with atherosclerotic lesions. One of ordinary skill in the art would have had a reasonable expectation of success in using the antisense compounds of Stinchcomb et al. to treat atherosclerosis because Stinchcomb et al. teach that antisense compounds that modulate CD40 expression can be used to treat disease.

Thus, the invention of claims 17, 18 and 23-27 would have been obvious, as a whole, at the time of invention.

Claims 17, 18, 23-26 and 62-67 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stinchcomb et al. as applied to claims 17, 18 and 23-26 above, and further in view of Tone et al. (PNAS 2001, vol. 98, pages 1751-1756) and Karras et al. (Biochemistry 2001, cited on IDS).

Claims 17, 18 and 23-26 are described in the previous 102 rejection. Claims 62-67 are directed to methods of redirecting splicing of CD40, reducing CD40 signaling or reducing IL-12 production in a cell using a CD40 antisense compound that does not activate RNAse H.

Stinchcomb et al. teach antisense oligonucleotides and ribozymes targeted to CD40 and a method of inhibiting CD40 in cells using these nucleic acids, see claims 1 and 24. At columns 5-8 under the heading 'Summary of the invention' Stinchcomb et al. teach that the methods of the invention can be used *in vivo* to treat disorders associated with CD40. At columns 1-5 Stinchcomb et al. teach that disorders associated with CD40 include immune disorders such as organ rejection, and inflammatory disorders such as psoriasis. Stinchcomb et al. do not teach that antisense compounds to CD40 can redirect splicing, reduce CD40 signaling or decrease IL-12 production.

Tone et al. teach that CD40 interactions with its ligand are associated with several diseases. Tone et al. further teach that CD40 has alternative splicing forms, including type I, which contains both an exodomain and a membrane-associated endodomain, and type II, which lacks the membrane-associated endodomain. CD40 signaling is controlled through alternative splicing by differential expression of the type I and type II isoforms in LPS activated cells: type I is expressed initially while at later times the level of type I decreases and type II is upregulated. Tone et al. also teach a relationship between the CD40 signaling associated with type I isoform and the presence of the type II isoform: cells transfected with the type II isoform decreased expression of endogenous CD40 and reduced the amount of transducible type I on the

cell surface. Tone et al. also teach a relationship between CD40 and IL-12 production: cells transfected with isoform type I showed enhanced expression of IL-12 while the presence of alternative forms of CD40 was found to downregulate expression of IL-12.

Karras et al. teach that antisense compounds that do not activate RNAse H can be used to redirect splicing of pre-mRNA. Karras et al. teach that such compounds have been previously used to redirect splicing of β-globin and exemplify their teaching using PNAs targeted to intron-exon junction regions of IL-5Rα. These antisense compounds have potential as therapeutics in diseases that are associated with aberrant splicing.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to use the antisense compounds taught by Stinchcomb et al. to redirect splicing of CD40 using a non-RNAse H activating antisense compound as taught by Karras et al. It would have been further obvious to use the redirected CD40 to modulate CD40 signaling and IL-12 production. Tone et al. provide a motivation to redirect splicing of CD40, teaching that differential expression of CD40 isoforms affects CD40 signaling and that expression of different isoforms of CD40 affects both CD40 signaling and IL-12 production. Karras et al. provide a motivation to use antisense compounds to redirect splicing by teaching that such alteration of splicing has therapeutic potential for diseases associated with aberrant splicing. One of ordinary skill in the art would have had a reasonable expectation of success in using antisense compounds of Stinchcomb et al. to redirect splicing because Karras et al. teach that

antisense compounds have been successfully used to redirect splicing and Stinchcomb et al. successfully used antisense compounds to modulate CD40 expression.

Thus, the invention of claims 17, 18, 23-26 and 62-67 would have been obvious, as a whole, at the time of invention.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Tracy Vivlemore whose telephone number is 571-272-2914. The examiner can normally be reached on Mon-Fri 8:45-5:15.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on 571-272-0811. The central FAX Number is 571-273-8300.

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center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Tracy Vivlemore
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TV
March 13, 2006

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